REMARKS

In accordance with the above amendments, claims 11 and 12 have been amended and claims 3, 4, and 39 have been withdrawn from consideration as being directed to a non-elected invention. Currently, claims 1-2, 5-6, 9-11, 17-26, 31-33 and 40-41 have been examined. Claims 12-16 have been objected to and have not been examined on the merits.

Claim Objections

Claims 12-16 stand objected to based on an improper multiple dependency form. This objection is believed to have been overcome by the amendment to claim 12 which now depends only on claim 11.

Specification

The hyperlink and/or other form of browser-executable code has been removed from page 22 in order to overcome the objection to the specification. Withdrawal of this rejection is respectfully requested.

Oath/Declaration

The Oath or Declaration was deemed defective because of alterations with regard to the signature of inventor Satu Vainikka. Accordingly, a new Declaration signed by Satu Vainikka, believed to be in compliance with 37 CFR 1.67(a), is being submitted with this paper.

Claim Rejections - 35 USC § 112

Claims 1-2, 5-6, 9-11, 17-26, 31-33 and 40-41 have been

rejected under 35 USC § 112, first paragraph, because, in the opinion of the Examiner, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims presented. This rejection is respectfully traversed. The Examiner is respectfully requested to consider the detailed explanation that follows:

1. *In vivo* delivery of the claimed molecules

The focus of the Examiner's rejection indicates the view that a skilled person would not be able to perform the claimed methods because there is no description of how molecules can be delivered *in vivo* to have a therapeutic effect.

The applicants believe a skilled person would have been well aware of approaches suitable for delivering the claimed molecules before the present application in view of the numerous publications in that field available prior to the 12 October 2001 priority date of the present application.

As an example, at that time, multiple pharmaco-kinetic and clinical studies had been published in relation to the Genasense antisense phosphorothioate oligonucleotide compound directed towards the human bcl-2 mRNA sequence, and termed Oblimersen.

As evidenced by the enclosed review article (Attachment "A") (Herbst and Frankel., 2004, *Clin. Cancer Res.*, 4245s-4248s), Oblimersen was an oligonucleotide that demonstrated "proof of principle of an antisense effect in human tumors" (see page

4246s, sentence bridging left- and right-hand columns). Those findings were first published in 2001 (see reference 30, referred to in Herbst and Frankel, 2004) and provide a clear demonstration that an antisense oligonucleotide can be delivered *in vivo* and have a therapeutic effect. Furthermore, Herbst and Frankel (2004) states that Oblimersen is "a drug that we know is pharmacologically deliverable … and we have some evidence in a large trial that it actually works" (see page 4247s, right-hand column).

Further evidence can be found in Klasa *et al.* (Attachment "B") (2001, *Antisense & Nucleic Acid Drug Development*, 12:193-213), a review article discussing the use of the Oblimersen antisense oligonucleotide. As stated on page 197, left-hand column, of that document the pharmacokinetics of Oblimersen were evaluated between 1999 and 2001 in which it was found that Oblimersen was consistently deliverable at a bioactive concentration in animals and achieved steady-state plasma concentrations when used to treat a range of cancer types.

For example, it is made clear that Oblimersen has been used to treat myeloid leukemias (see page 203), chronic lymphocytic leukemia (see pages 203-204), solid tumors (see pages 204-205), prostate cancer (see page 206), colorectal cancer (see page 207) and lung cancers (see pages 207-208), among others; in each case, it is noted that Oblimersen demonstrated anticancer activity *in vivo* (i.e. in clinical trials) demonstrating that it was

successfully delivered. Throughout that document, and in spite of the large number of different clinical and experimental anticancer trials described, no mention is made of any difficulties in delivering the antisense-based Oblimersen drug to the correct tissues or in achieving an effective concentration *in vivo*.

Such findings are also seen in Yang et al. and Resnicoff et al. (Attachment "C") (1999, *Proc. Am. Assoc. Cancer Res.*, 40: 4814 and 4816, respectively). Yang et al. describes the antitumor effect of Oblimersen in treating human breast carcinoma, reporting that "treatment with G3139 (i.e. Oblimersen) alone can inhibit tumor formation *in vivo*". On the same page of that journal article, Resnicoff et al. report the clinical trial of an antisense oligonucleotide to the IGF-1 receptor and that such treatment resulted in complete remission of malignant glioma in two patients of the twelve tested.

Finally, van de Donk et al. (Attachment "D") (2000, *Blood*, 96:757a) reports that evaluation of the Genasense antisense drug in multiple myeloma, concluding that the observed significant reduction of Bcl-2 protein levels *in vivo* following treatment indicates that the agent will be useful in myeloma therapy.

Clearly then, applicants submit that there is ample evidence that it is possible to deliver an oligonucleotide-based drug in a manner capable of achieving an *in vivo* therapeutic effect and that such approaches were being taken before the priority date of

the present application. In light of those prior art teachings, applicants submit that a skilled person would have been able to achieve delivery of the presently claimed compounds without undue difficulty and without a specific teaching in the present application.

The Examiner has cited a number of documents in an effort to support her allegation and takes the view that they provide evidence that it was not possible to achieve the *in vivo* delivery of oligonucleotide drugs. However, we think that those documents make it clear that it was actually possible to deliver oligonucleotide-based compounds *in vivo*.

For example, Chirila et al. (2002, *Biomaterials*, 23:321-342) states in the introduction that "at least a dozen human clinical trials with antisense oligonucleotides have been initiated since 1992" (see page 322, right-hand column), clearly indicating that approaches were indeed available that were capable of delivering oligonucleotides *in vivo*. Furthermore, as evidenced by page 322 of Chirila et al. (2002), at least one such antisense oligonucleotide drug had been successful in clinical trials and was subsequently approved by the FDA in 1998 for the treatment of cytomegalovirus retinitis.

The Examiner notes that Chirila et al. (2002) states that a drawback of using antisense oligonucleotides is finding an adequate delivery method, however, Chirila et al. (2002) also makes it clear that a number of solutions have been developed to

deal with that problem. Accordingly, from Chirila et al. (2002), it appears that the problem alleged by the Examiner had, insofar as it exists, already been effectively addressed prior to the present application.

Furthermore, Chirila et al. (2002) makes it clear that there is skepticism that delivery systems are even required for delivering antisense oligonucleotides, and notes that such oligonucleotides can be delivered without any carrier and still display antisense activity (see page 327, right-hand column). It is further stated that a therapeutic effect can be achieved by repeatedly administering such oligonucleotides even without the use of a specific delivery system (see page 327, right-hand column).

The remaining documents cited by the Examiner, Opalinska et al. (2002, *Nature Reviews*, 1:503-514) and Jen et al. (2000, *Stem Cells*, 18:307-319), also make reference to successful attempts by workers in the antisense field to deliver oligonucleotides *in vivo* and which have subsequently undergone clinical trials or FDA approval (see Opalinska, page 512, right-hand column and Jen, page 315, right-hand column).

In view of the above, applicants consider that a skilled person would be able to perform the presently claimed methods without undue difficulty.

2. Structure of the claimed molecules

It is the Examiner's view that the application does not meet

the written description requirement because the claims encompass a broad range of molecules that are not supported by the examples. The applicants respectfully traverse this position.

In regard to this issue and also in further support of enablement, a 2006 decision by the Court of Appeals for the Federal Circuit in *Falkner v Inglis* (448 F.3d 1357 C.A. Fed. 2006) applicants believed, fully supports the premise that the claims meet the written description requirement.

The Court clearly held (at 1366) that a claim would not be invalidated on Section 112 written description grounds simply because the application did not contain examples covering the full scope of the claim language. Because the specification is directed to a person skilled in the art, such a person is credited with the knowledge of what has come before. Only enough must be included to convince a person skilled in the art how to make and use the invention without undue experimentation and even routine experiments are quite complex. The decision also makes it clear that actual reduction to practice is not required.

The definitive question to be answered is whether the concept of the invention was complete and exemplified in the application.

In the present case, the examples make it clear that the inventors had developed methods for modulating or suppressing gene expression as claimed in claims 1 and 2 by introducing a molecule comprising a nucleic acid-binding portion of an

oligonucleotide or oligonucleotide mimic and an expression modulating portion comprising a polypeptide or peptidomimetic. Indeed, the Examiner acknowledges in the Office Action that Examples 8, 9 and 10 of the application demonstrates the use of oligo/peptide fusion molecules to reduce expression of various genes in cell culture.

Accordingly, we think that the inventors were in possession of the presently claimed invention and that the examples in the application provide sufficient information for the skilled person to perform the subject matter of the claims.

In view of the above amendments, taken together with the explanatory remarks presented, the Examiner is respectfully requested to reconsider her position and withdraw the objections and rejections contained in the Office Action.

Early consideration of this paper and allowance of the claims is respectfully requested.

Respectfully submitted,

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CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that the foregoing Amendment in response to an Official Action of May 24, 2007, a Supplemental Declaration, Attachment "A", "B", "C", "D" and a Petition for a one-month extension of time in application Serial No. 10/824,584, filed on April 8, 2004, of Stephen Hart et al, entitled "CONTROL OF GENE EXPRESSION USING A COMPLEX OF AN OLIGONUCLEOTIDE AND A REGULATORY PEPTIDE", and a transmittal letter are being sent by facsimile transmission to: The Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on September 11, 2007.

Barbara L Davis

Barbara L. Davis
On behalf of C. G. Mersereau

Date of Signature: September 11, 2007